Pivotal PFO Stroke Trials

Update I: RESPECT
Long-term Follow-up Data

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Disclosure Statement of Financial Interest

Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below.

Affiliation/Financial Relationship	Company
• Grant/Research Support	• AstraZeneca (TRACTOR Migraine Trial)
• Consulting Fees/Honoraria	• WL Gore (HELICOPTER Trial) • Abbott / St Jude • Boston Scientific

All TCT 2017 faculty disclosures are listed online and on the app.

Background: 1988

1148 THE NEW ENGLAND JOURNAL OF MEDICINE May 5, 1988

PREVALENCE OF PATENT FORAMEN OVALE IN PATIENTS WITH STROKE

PH. LECHAT, M.D., PH.D., J.L. MAS, M.D., G. LASCAULT, M.D., PH. LORON, M.D., M. THEARD, M.D., M. KLIMCZAC, M.D., G. DROBINSKI, M.D., D. THOMAS, M.D., AND Y. GROSGOGEAT, M.D.

THE LANCET, JULY 2, 1988

PATENT FORAMEN OVALE IN YOUNG STROKE PATIENTS

M. W. I. WEBSTER, A. M. CHANCELLOR, H. J. SMITH, D. L. SWIFT, D. N. SHARPE, N. M. BASS, G. L. GLASGOW

Departments of Medicine, Neurology, and Cardiology, Auckland Hospital, Auckland, New Zealand

- ✓ Incidence of PFO in cryptogenic stroke patients < 55 years of age = 40 – 60%
- ✓ In contrast to 20 – 25% in general population

Lechat et al. NEJM 1988; Webster et al. Lancet 1988.

Background: 1992

- ✓ As an alternative to blood thinners, a PFO could be closed with a minimally invasive transcatheter technique (with pediatric ASD closure devices).

Transcatheter Closure of Patent Foramen Ovale After Presumed Paradoxical Embolism

Nancy D. Bridges, MD; William Hellenbrand, MD; Larry Latson, MD; James Filiano, MD; Jane W. Newburger, MD; and James E. Lock, MD

Circulation 1992;86:1902-1908

- ✓ Developed tremendous traction as an “off-label” procedure

PFO – Stroke History

Heated Debate for > 20 Years

Stroke Neurologists

Interventional Cardiologists

Does PFO Closure Work Better than Blood Thinning Medication?

Trial Design

- Multicenter: 69 Sites (62 US, 7 Canada)
- Prospective, randomized 1:1, unblinded, stratified by site/ASA
  - Device Cohort: Closure with the AMPLATZER™ PFO Occluder plus medical therapy
  - Medical Therapy Cohort: One of 5 pre-specified regimens
    - Aspirin Alone, Warfarin Alone, Clopidogrel Alone, Aspirin/Dipyridamole
    - Aspirin/Clopidogrel (discontinued in 2006 with AHA/ASA guideline changes)
- Sample size: Event driven, enrolled until the 25th endpoint
- Ongoing follow-up until an FDA Regulatory Decision
- Conducted under an IDE by St. Jude Medical*

*Initiated by AGA Medical

Trial Design

- Primary endpoint was a composite of:
  - Recurrent nonfatal ischemic stroke
  - Fatal ischemic stroke
  - Early post-randomization death (within 45 days)
- Cryptogenic stroke definition:
  - Acute focal neurological deficit due to cerebral ischemia with:
    - Neuro-anatomically relevant infarct on imaging or with symptoms >24hr
    - **AND**, other stroke sources excluded by “cryptogenic” evaluation

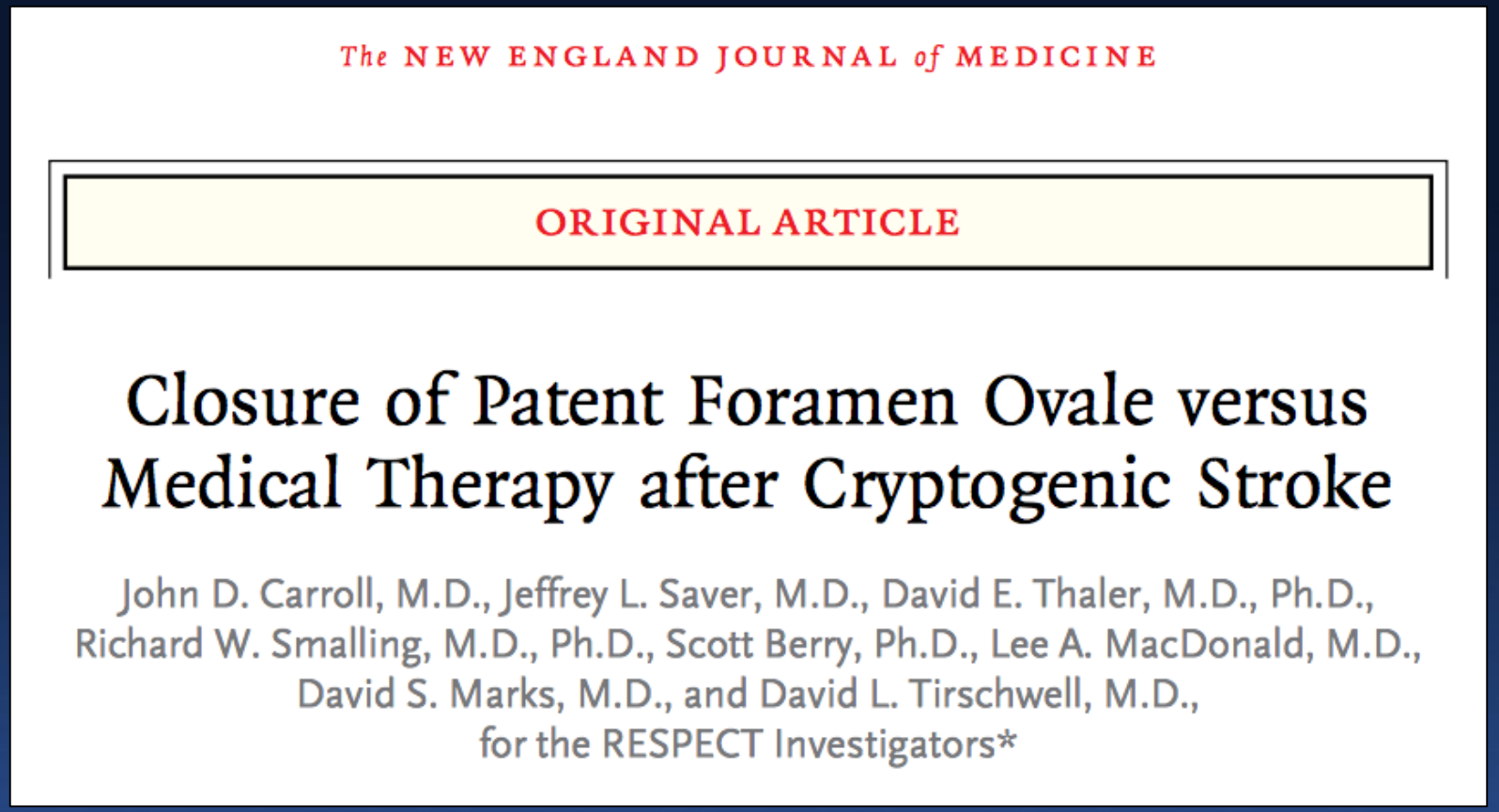
Trial Design

- Inclusion:
  - Patients (ages 18 – 60) with PFO, who have had a cryptogenic stroke within 270 days
  - PFO defined as TEE visualization of micro-bubbles in the left atrium within 3 cardiac cycles at rest and/or during Valsalva release
- Exclusion:
  - Other potential source of stroke
  - Contraindication to anti-thrombotic therapy
  - Anatomic contraindication to device placement

Trial Design

- Pre-specified Analyses:
  - Intent to treat of the Raw Count Cohort
  - If unequal drop-out occurred, invalidating the ITT analysis, then:
    - “As Treated” Analysis
    - “Per Protocol” Analysis

Publication of Initial Data 2013



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Closure of Patent Foramen Ovale versus Medical Therapy after Cryptogenic Stroke

John D. Carroll, M.D., Jeffrey L. Saver, M.D., David E. Thaler, M.D., Ph.D., Richard W. Smalling, M.D., Ph.D., Scott Berry, Ph.D., Lee A. MacDonald, M.D., David S. Marks, M.D., and David L. Tirschwell, M.D., for the RESPECT Investigators*

Carroll et al. N Engl J Med 2013;368:1092-100

Initial Trial Results 2013

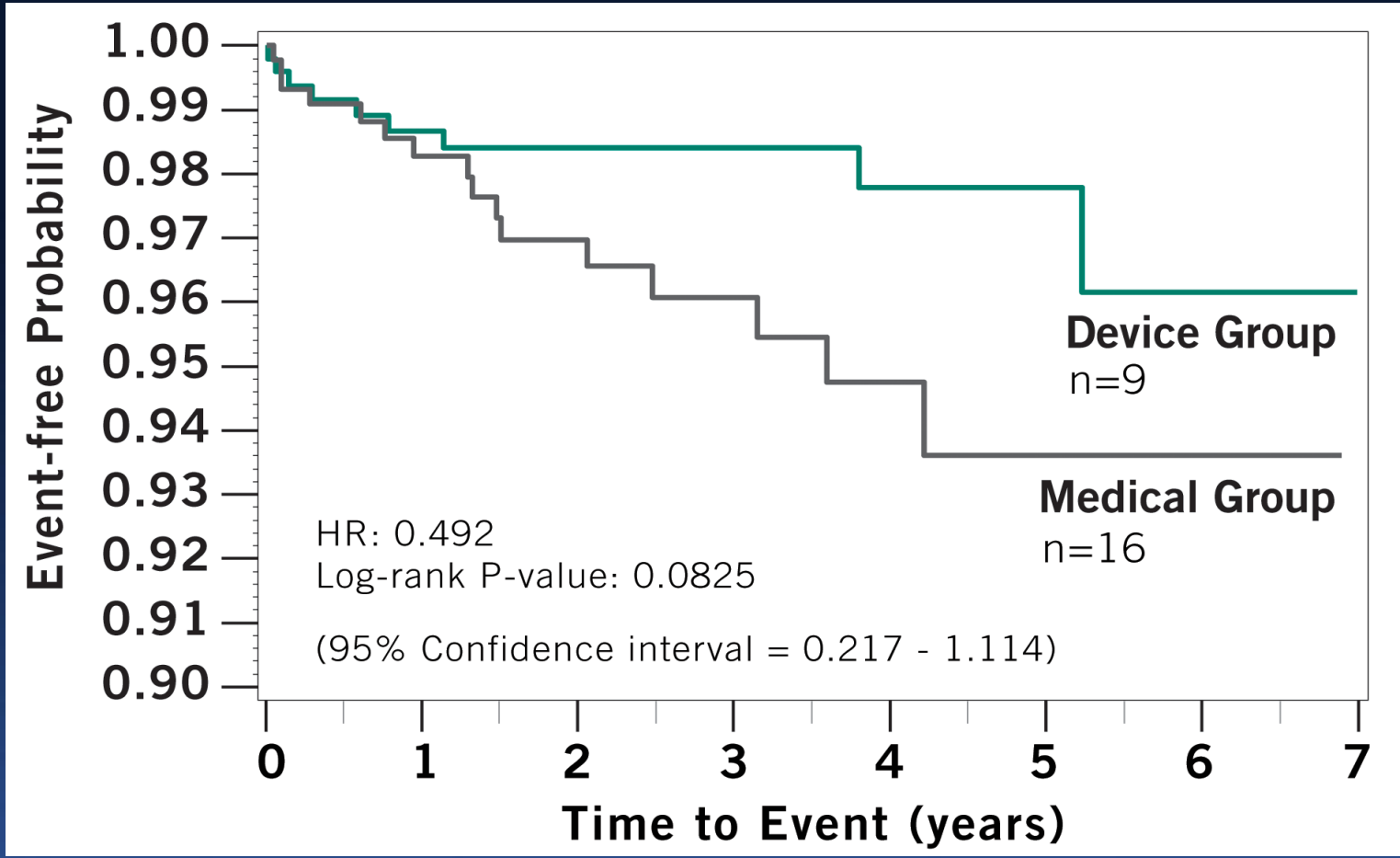
- 980 patients enrolled (2003 – 2011) prior to 25th endpoint with a 2.1 yr mean follow-up. 499 closure/481 medical.

Patient Characteristics	AMPLATZER™ PFO Occluder (N=499)	Medical Management (N=481)
Age (yr), mean ± SD	48 ± 10	46 ± 10
Male	54%	56%
Hypercholesterolemia	39%	41%
Family h/o CAD	33%	33%
Hypertension	32%	32%
COPD	0.8%	1.5%
Congestive heart failure	0.6%	0%
History of DVT	4.0%	3.1%
Atrial septal aneurysm	36%	35%
Substantial shunt	50%	48%

- 99% success rate in attempted implantation

Carroll et al. N Engl J Med 2013;368:1092-100

Primary Endpoint Analysis – ITT Cohort 2013

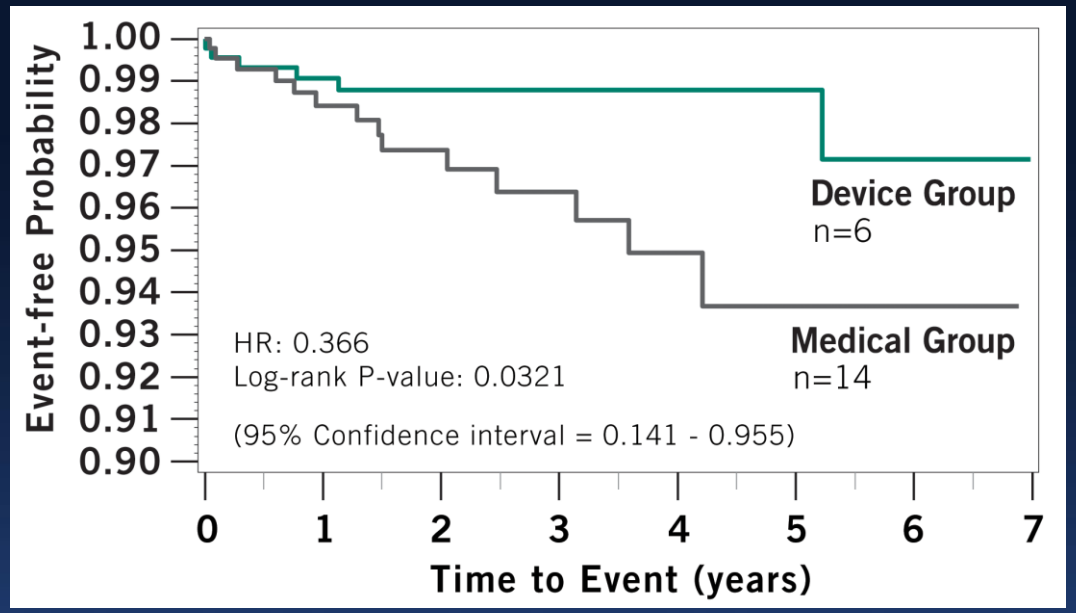


- All endpoints were recurrent nonfatal ischemic strokes.
- 50.8% risk reduction in favor of device group (p > 0.05)
- 3/9 device cohort endpoints occurred in patients who did not have a device at the time of the endpoint
- Unequal drop-out over trial (33% Medical Arm, 21% Closure)

Carroll et al. N Engl J Med 2013;368:1092-100

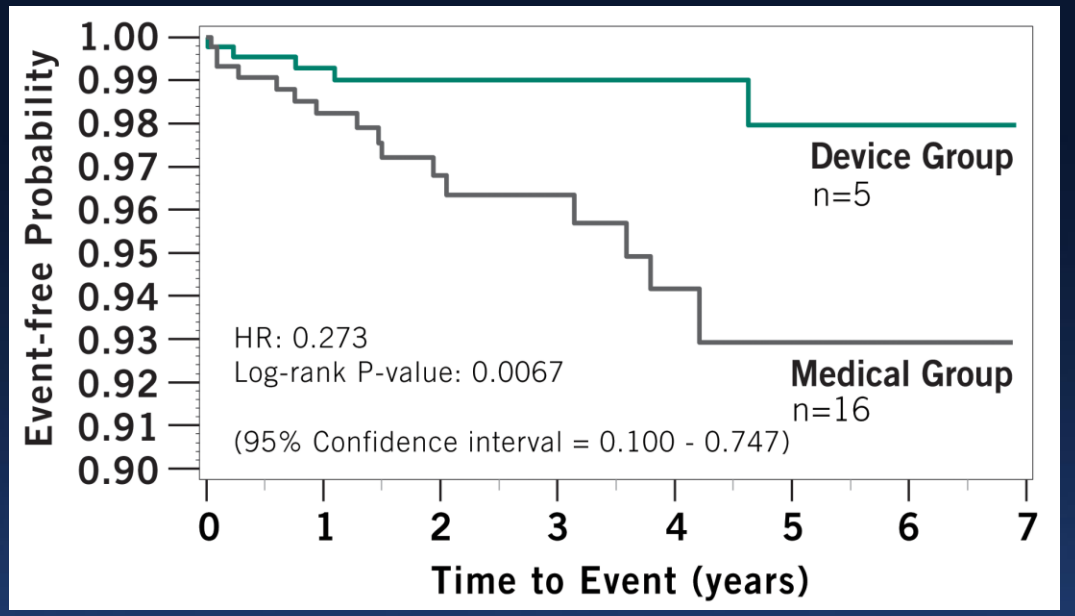
Primary Endpoint Analysis – Secondary Analyses

Per Protocol



- Included all pts who adhered to the requirements of the protocol

As Treated



- Patients grouped based on actual treatment received, regardless of cohort assignment

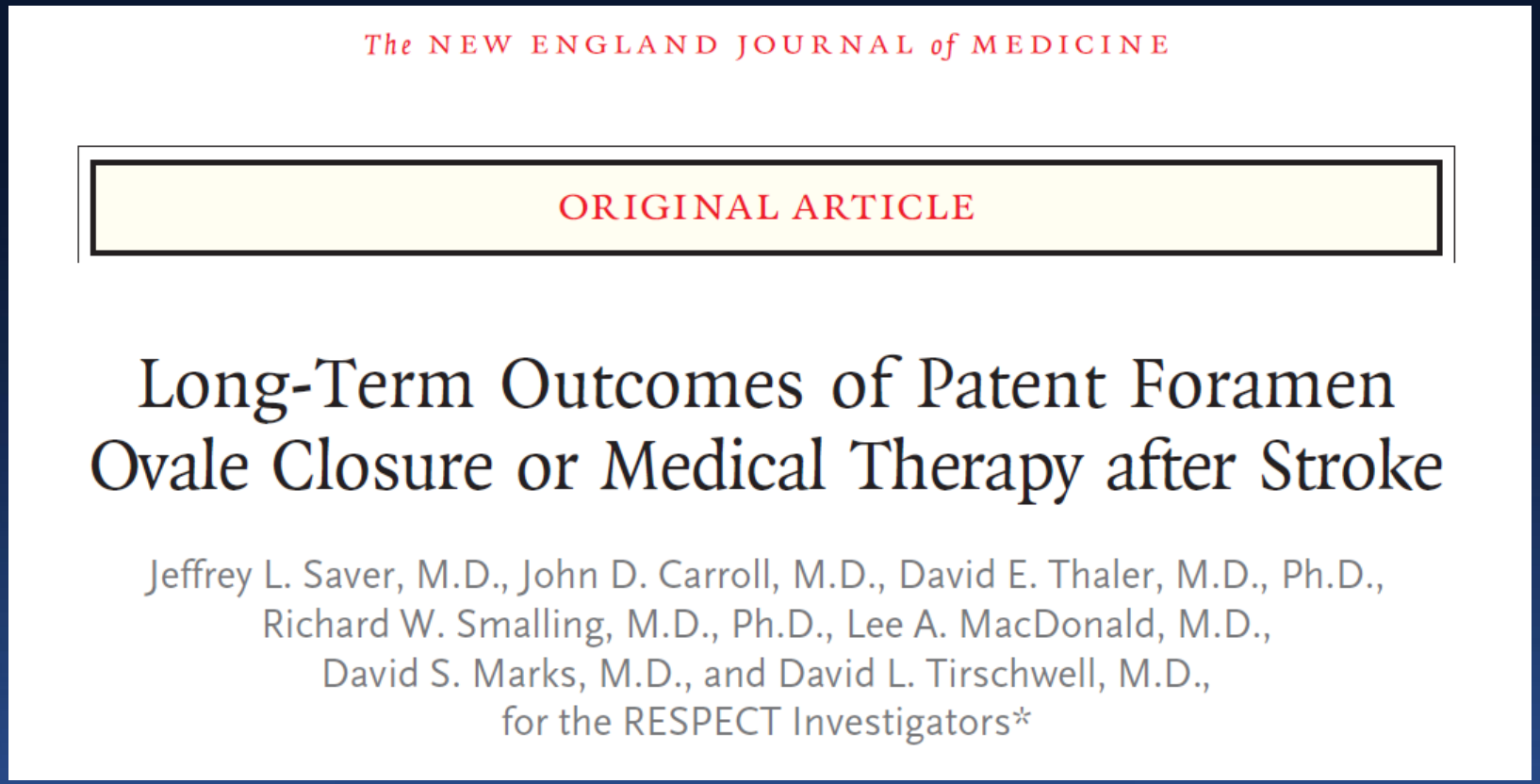
Carroll et al. N Engl J Med 2013;368:1092-100

RESPECT 2013

- In the ITT population, initial data point estimates favored closure but did not reach statistical significance
- RESPECT protocol required follow-up until an FDA regulatory decision (data lock at August 2015 – 5.9 yr mean f/u)
- The FDA requested a post-hoc analysis of long-term outcomes
  - Recurrent ischemic strokes adjudicated by a blinded Clinical Events Committee
  - Recurrent ischemic strokes of unknown mechanism, cause adjudicated by a blinded committee of neurologists and a neuro-radiologist

Publication of Long-Term Data

Mean follow-up = 5.9 years



The NEW ENGLAND JOURNAL of MEDICINE

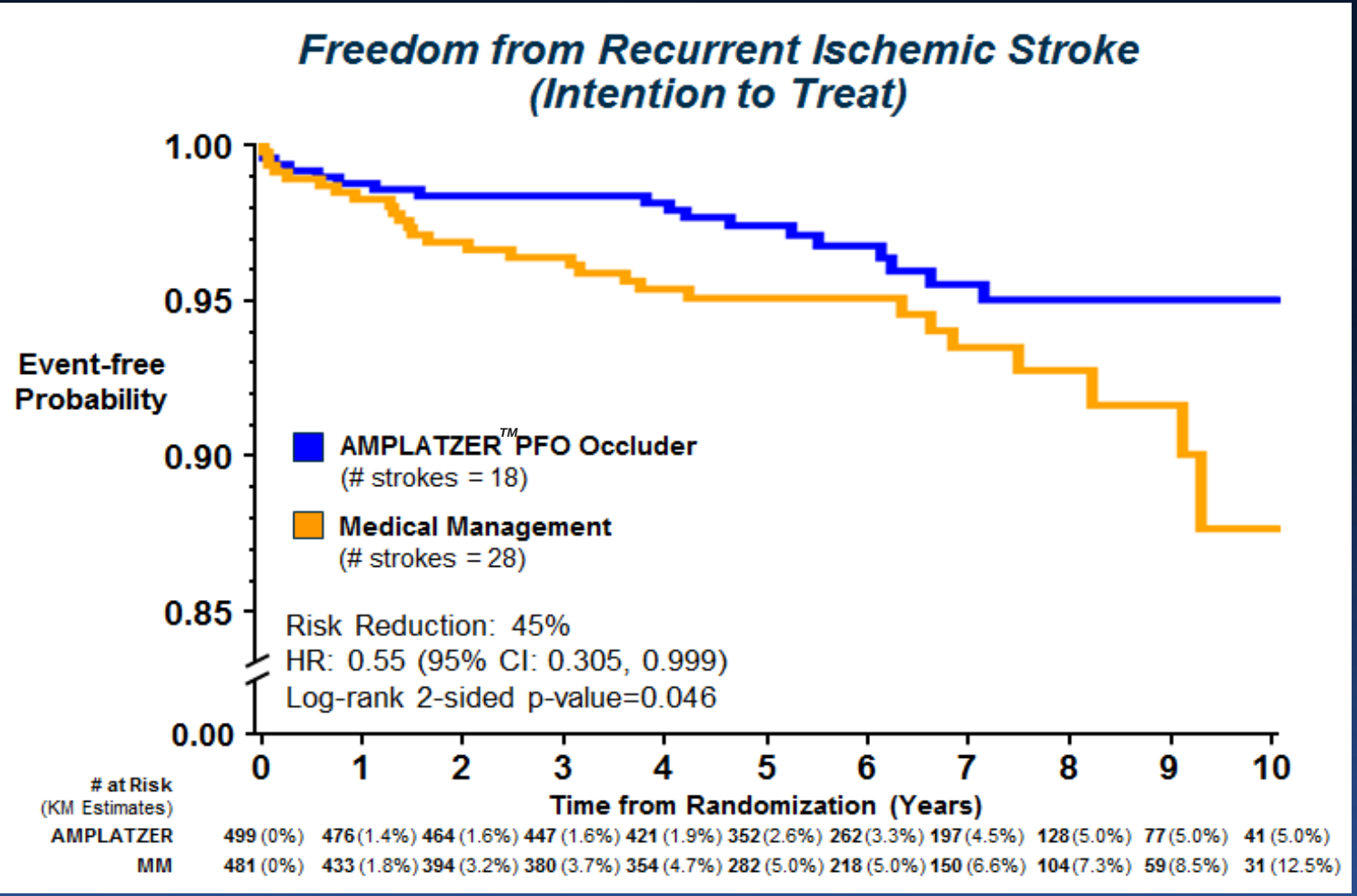
ORIGINAL ARTICLE

Long-Term Outcomes of Patent Foramen Ovale Closure or Medical Therapy after Stroke

Jeffrey L. Saver, M.D., John D. Carroll, M.D., David E. Thaler, M.D., Ph.D., Richard W. Smalling, M.D., Ph.D., Lee A. MacDonald, M.D., David S. Marks, M.D., and David L. Tirschwell, M.D., for the RESPECT Investigators*

Saver et al. N Engl J Med 2017;377:1022-32.

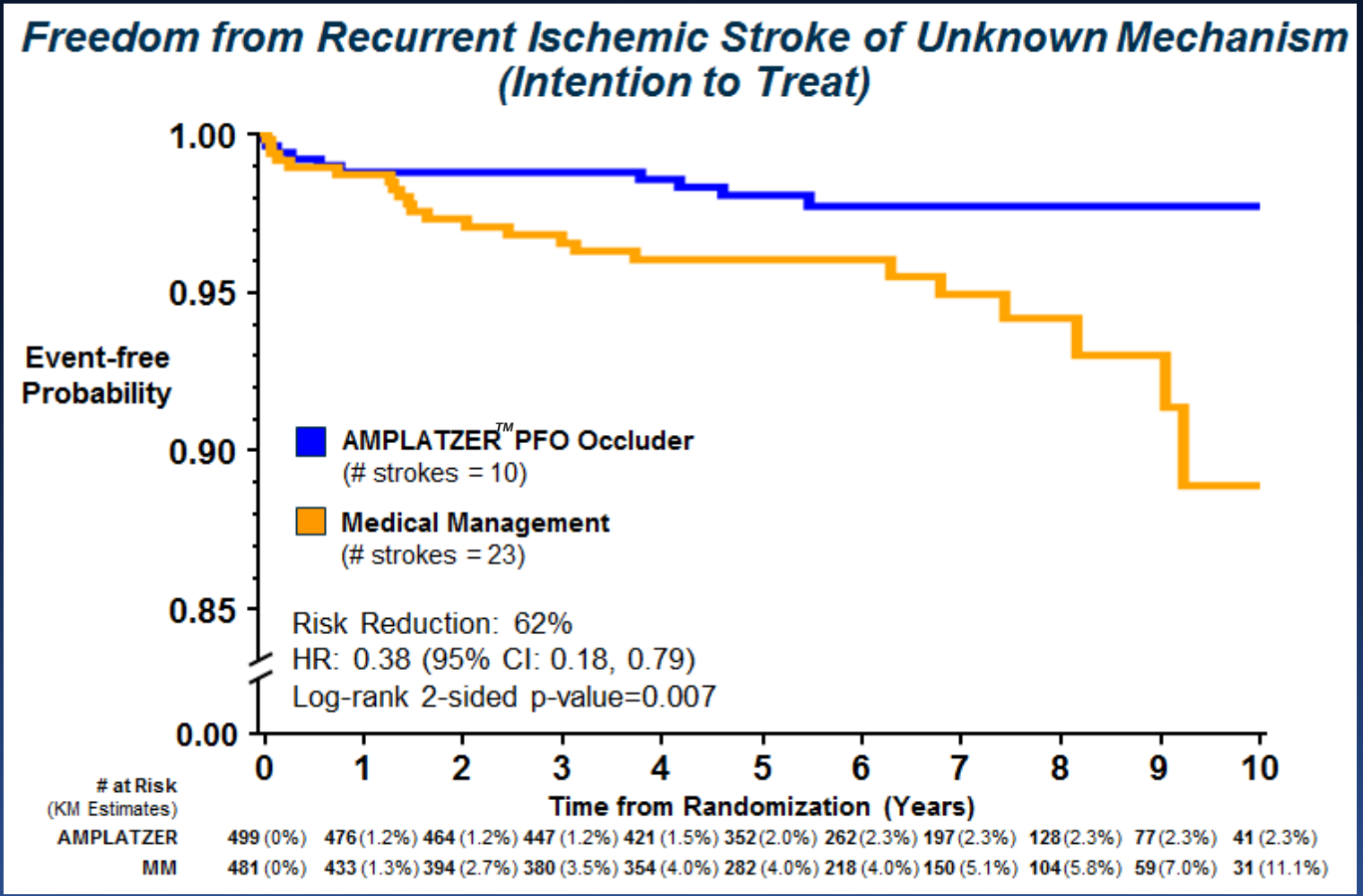
Primary Endpoint Analysis – Long-term ITT Data



- Mean f/u = 5.9 yrs
- All endpoints were recurrent non-fatal ischemic stroke
- 45% relative risk reduction in favor of device group in the intent to treat cohort
- P < 0.05

Saver et al. N Engl J Med 2017;377:1022-32.

Primary Endpoint Analysis – Long-term Data



- 13 pts excluded from prior analysis due to “defined” non-PFO mechanism of ischemic stroke
- 62% risk reduction in favor of device group in the intent to treat cohort
- P = 0.007

Saver et al. N Engl J Med 2017;377:1022-32.

SAE's – Adjudicated by DSMB

Excellent Safety Record

- ✓ No intra-procedural stroke
- ✓ No device embolization
- ✓ No device thrombosis
- ✓ No device erosion
- ✓ Vascular complications 0.9%
- ✓ Device explants 0.4%
- ✓ Atrial fibrillation – 1.6%, not different than medical arm
- ✓ Major bleeding – 3.6%, not different than medical arm

Saver et al. N Engl J Med 2017;377:1022-32.

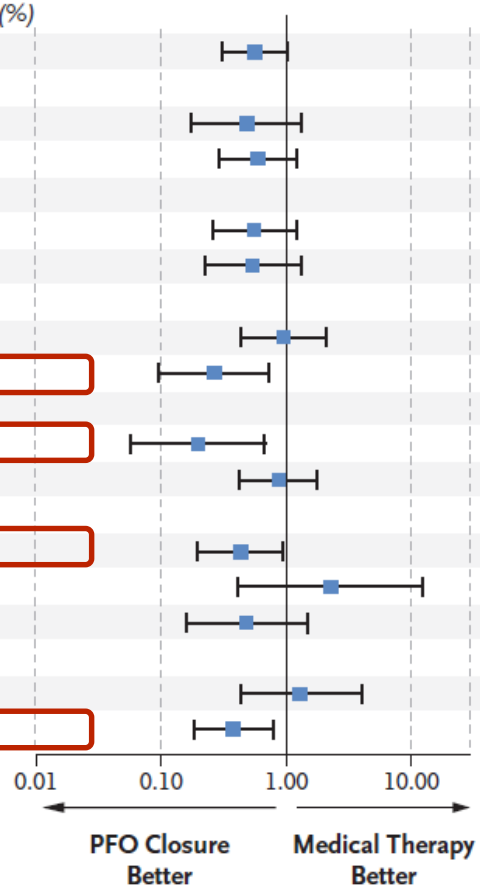
RESPECT Final Results

- ✓ SAEs (adjudicated by DSMB):
  - DVT/PE greater in Device cohort
    - 18 vs. 4, p = 0.006
    - Particularly in patients with prior hx of DVT/PE
    - May be explained in part by differences in OAC use, < 2% in device cohort, ~20% in medical cohort

Saver et al. N Engl J Med 2017;377:1022-32.

Sub-group Analysis – Heterogeneity in Rx Effect

Subgroup	PFO Closure Group	Medical-Therapy Group	Hazard Ratio (95% CI)	P Value by Log-Rank Test	P Value for Interaction
	no. of patients with event/total no. (%)				
Overall	18/499 (3.6)	28/481 (5.8)	0.55 (0.30–1.00)	0.046	
Age					0.78
18–45 yr	6/230 (2.6)	10/210 (4.8)	0.49 (0.18–1.35)	0.16	
46–60 yr	12/262 (4.6)	18/266 (6.8)	0.59 (0.28–1.23)	0.16	
Sex					1.00
Male	10/268 (3.7)	16/268 (6.0)	0.56 (0.25–1.23)	0.14	
Female	8/231 (3.5)	12/213 (5.6)	0.55 (0.22–1.34)	0.18	
Shunt size					0.04
None, trace or moderate	13/247 (5.3)	12/244 (4.9)	0.96 (0.44–2.11)	0.93	
Substantial	5/247 (2.0)	16/231 (6.9)	0.26 (0.10–0.71)	0.005	
Atrial septal aneurysm					0.04
Present	3/179 (1.7)	13/170 (7.6)	0.20 (0.06–0.70)	0.005	
Absent	15/320 (4.7)	15/311 (4.8)	0.86 (0.42–1.76)	0.68	
Index infarct topography					0.21
Superficial	9/280 (3.2)	18/269 (6.7)	0.43 (0.19–0.96)	0.03	
Small deep	4/57 (7.0)	2/70 (2.9)	2.25 (0.41–12.32)	0.34	
Other	5/157 (3.2)	8/140 (5.7)	0.48 (0.16–1.48)	0.19	
Planned medical regimen					0.07
Anticoagulant	8/132 (6.1)	5/121 (4.1)	1.32 (0.43–4.03)	0.63	
Antiplatelet	10/367 (2.7)	23/360 (6.4)	0.38 (0.18–0.79)	0.007	



- **Larger shunt predicted better outcome with closure as did presence of ASA**
- **Superficial baseline infarct location**
- **Planned use of antiplatelet agent favored closure**

RESPECT – Conclusions

- ✓ In an analysis of patients 18 to 60 years of age at the time of an index cryptogenic ischemic stroke, PFO closure with the Amplatzer PFO Occluder was associated with a lower rate of recurrent ischemic stroke than medical therapy alone, during an extended follow-up period.
- ✓ Led to FDA approval of device on 10/28/2016 after 25 years of debate.
- ✓ There was a higher rate of VTE in the closure cohort.
- ✓ In this dataset, there appeared to be some treatment effect heterogeneity, with potential statistical benefit in those with larger R to L shunt, ASA, and superficial cerebral infarct. These observations will present opportunities for further research.